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Early Bactericidal Activity of High-Dose Rifampin in Patients with Pulmonary Tuberculosis Evidenced by Positive Sputum Smears[▽]

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We studied the early bactericidal activity of twice the standard dose of rifampin in subjects with pulmonary tuberculosis evidenced by positive smears. The observed mean 2-day activity was almost double that reported at the standard dose. Further studies are warranted to establish whether higher rifampin doses might assist in shortening tuberculosis treatment.

Rifampin (RMP) is a key drug in standard antituberculosis regimens. The sterilizing properties of RMP in conjunction with pyrazinamide lay the foundation for the current "short-course" 6-month regimens (11). The standard RMP dose of 8 to 12 mg/kg of body weight (21) is probably at the lower limit of optimal efficacy (11, 13, 18, 20), but it is not clear whether higher doses of RMP could increase its activity (12). We studied the pharmacokinetics and the 2-day and 5-day early bactericidal activities (EBA) of RMP at a dose of 20 mg/kg of body weight.

We included treatment-naïve patients with pulmonary tuberculosis, evidenced by positive smears, who had no past history of liver disease and normal serum transaminase and bilirubin levels. RMP was given daily over five days in a single dose before breakfast. Patients were monitored for unexpected signs and symptoms for 7 days in the hospital and again 2 weeks after the last dose of study medication. Sixteen-hour sputum specimens were collected overnight before and over 5 days after initiation of treatment. Patients commenced standard antituberculosis treatment on discharge. The Committee for Pharmaceutical Trials of the University of Stellenbosch and the South African Medicines Control Council approved the study. All patients gave written informed consent.

After sputum digestion (Sputasol; Oxoid Ltd., Poole, England) and homogenization, two series of 10-fold dilutions were incubated on selective 7H10 agar plates for the enumeration of CFU as described previously (17). Serum samples were taken at 1, 1.5, 2, 2.5, 3, 4, 8, 12, and 24 h after the first dose. RMP concentrations were measured by high-pressure liquid chromatography with UV detection as previously described (17). The EBA was defined as $(Z_0 - Z_D)/D$, where Z_0 and Z_D are logarithms of the CFU counts per ml sputum prior to the start of treatment and after D days of treatment, respectively (17). All data are displayed as mean ± standard deviations unless stated otherwise.

One of 14 enrolled patients was excluded following an episode of hemoptysis. Thirteen patients whose sputum was at least 2+ smear positive for acid-fast bacilli completed the study (age, 27 ± 9 years; 61% male; body weight, 55 ± 16 kg). On chest radiography, all patients had at least one cavity, and 7 (54%) had bilateral disease. Three patients (23%) were human immunodeficiency virus positive. Clinically observed adverse events were mild and transient. One patient suffered a secondary pneumothorax 2 weeks after discharge and received pleural drainage. No other serious adverse events occurred during the study or were evident at the 2-week follow-up.

All strains isolated were susceptible to RMP (Bactec MGIT 960 SIRE kit; Becton Dickinson, Sparks, MD). The mean initial *Mycobacterium tuberculosis* CFU count was 7.0 ± 0.4 $\log_{10}$/ml sputum. The 2-day and 5-day EBA of rifampin at 20 mg/kg were 0.44 ± 0.24 and 0.30 ± 0.11 $\log_{10}$ CFU/ml sputum, respectively. Figure 1 illustrates the 0- to 5-day EBA, and Fig. 2 illustrates the 0- to 2-day EBA in the present study in relation to previous studies of the EBA of RMP performed at centers in Hong Kong; Nairobi, Kenya; and South Africa (3, 6, 15–17). Table 1 shows the pharmacokinetics of RMP at 20 mg/kg as used in the present study compared to doses of 3 mg/kg, 6 mg/kg, and 12 mg/kg given to a similar population in an earlier EBA study analyzed at the same laboratory (17). The maximum drug concentration found in that study was unexpectedly high for an RMP dose of 600 mg and did not differ from that in the present study (14.0 versus 13.6 μg/ml). However, the area under the curve in the present study was significantly greater than that after an RMP dose of 600 mg (171 versus 100 μg · h/ml; $P < 0.01$ by z test). It is generally accepted that the first-pass excretory capacity of the liver for RMP is saturated at doses above 450 mg (1), so a proportional increase of the pharmacokinetic parameters from 600 mg to 1,200 mg could be expected. The mean 2-day EBA at an RMP dose of 20 mg/kg was also almost double that found at a dose of 600 mg RMP (0.439 versus 0.221 $\log_{10}$ CFU/ml sputum; $P = 0.02$ by z test).

The main finding of this study is the near-linear increase of

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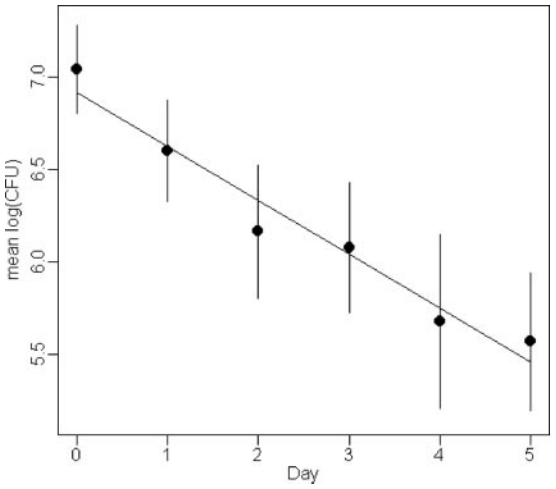

FIG. 1. Serial sputum mean log CFU counts over 5 days of treatment with RMP at 20 mg/kg of body weight. Data are means ± 2 standard errors. There is no strong evidence of departure from a linear trend, as indicated by the fitted straight line.

the 2-day bactericidal activity of RMP with a dose double that used in standard antituberculous treatment (21). Previous evidence for a dose-related response to the action of RMP was provided by both animal experiments and clinical trials with doses of up to 20 mg/kg RMP (3, 5, 10, 15, 17, 19). An earlier EBA study published more than 25 years ago (6) found a similar high EBA at an RMP dose of 20 mg/kg of body weight, but high cost, the propensity of RMP for drug-drug interactions, and fears of hepatotoxicity might have precluded the further exploration of above-standard RMP doses. Indeed, increased serum transaminase concentrations as well as increased bilirubin levels after starting RMP treatment are common, but these do not appear to be dose related (7, 14). Severe

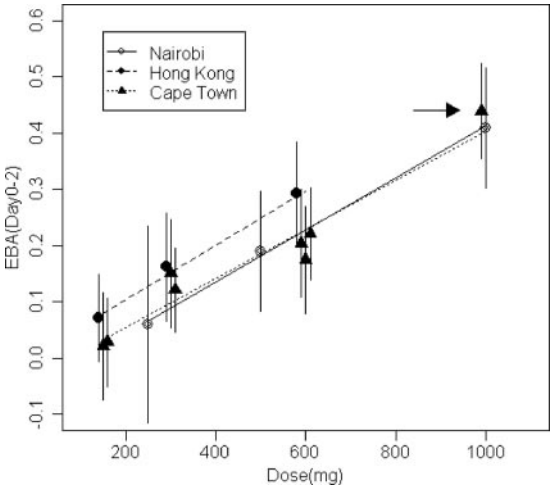

FIG. 2. EBA data from studies performed in Hong Kong (3), Nairobi (6), and Cape Town (15–17), including the present study (arrow). For comparison, the doses of RMP are normalized to a patient weighing 50 kg. Data are means ± 2 standard errors. The standard error is calculated using a pooled estimate of standard deviation from all studies, where available, and the number of subjects in the study.

TABLE 1. Pharmacokinetics of rifampin at doses of 3 mg/kg, 6 mg/kg, and 12 mg/kg of body weight during a previous study (17) and at 20 mg/kg of body weight during the present study[a]

RMP dose (mg/kg)	*n*	C_{max} (μg/ml)	T_{max} (h)	AUCI (μg · h/ml)
3	8	2.53 (1.95)	3.12 (2.63)	13.1 (4.5)
6	8	3.19 (1.58)	3.67 (2.63)	24.5 (8.8)
12	8	13.0 (4.5)	2.50 (2.46)	100 (21)
20	13	14.0 (4.7)	3.27 (2.1)	171 (56)

[a] C_{max}, peak concentration; T_{max}, time to peak concentration; AUCI, area under the concentration-time curve extrapolated to infinity. All values are means (standard deviations).

hepatotoxicity associated with the use of RMP has only rarely been reported to occur in the elderly and those with preexisting liver disease (8, 9). Interestingly, RMP at a dose of 900 mg has been used for 45 days to treat brucellosis without evidence of toxicity (2). Systemic side effects such as the "flu-like-syndrome" seem to be related to intermittent treatment rather than to the dose of RMP (4, 12). As EBA studies reflect bactericidal and not necessarily sterilizing activity, more studies are needed to evaluate the potential of a higher dose of RMP to further reduce treatment duration to less than 6 months. Evidence of this potential is provided by the study of Kreis et al. (7), who evaluated a 3-month regimen with daily RMP (1,200 mg), isoniazid (900 mg), and streptomycin (1 g) and achieved near-complete sputum culture negativity after 90 days, without additional toxicity. The recurrence rate was 11.4% during the first year after treatment. It is reasonable to speculate that the additional use of pyrazinamide could further reduce the relapse rate documented by Kreis et al. (7). The maximum effective dose of RMP remains to be determined.

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